Vaccine: X 18 (2024) 100487

Contents lists available at ScienceDirect

Vaccine: X

journal homepage: www.elsevier.com/locate/jvacx

Antibody responses to SARS-CoV-2 spike protein in a cohort of renal transplant recipients following two-dose primary immunization – A Caribbean country's perspective

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ARTICLE INFO

Keywords:
Immunization
COVID-19
Renal transplantation recipients
Trinidad & Tobago
Non-mRNA vaccines
Anti-spike protein antibodies

ABSTRACT

This study compares the humoral immune response of a cohort of renal transplant recipients (RTRs), in Trinidad & Tobago following two-dose primary immunization with non-mRNA vaccines amidst the COVID-19 pandemic. RTRs along with healthy, age-and gender-matched controls received either the adenoviral vector vaccine, AstraZeneca-Vaxzevria (AZ) or the inactivated vaccine, Beijing CNBG-BBIBP- CorV/Sinopharm (SP). Samples were taken after completion of a two-dose primary immunization during the period November 2021 to December 2021, at a mean interval of 138 days following immunization.

38/72 RTRs (53 %) failed to generate any protective antibody responses, compared with 7/73 participants, approximately 10 % in the healthy, age and gender-matched control group. In the RTRs, there was no significant correlation of their antibody concentration with either the timing of sample collection or the interval since transplantation.

The study provides necessary information about the humoral response after two- doses of non-mRNA vaccines in a group of transplant recipients.

Introduction

In 2021, during the COVID-19 pandemic, the twin-island Republic of Trinidad and Tobago at the southernmost tip of the Caribbean archipelago, experienced surges in COVID-19-related hospitalizations and deaths linked to successive spread of Gamma, Delta, and Omicron strains of SARS-CoV-2 virus [1].

Vaccines were considered the best option to curtail the severity of infections and reduce the number of hospitalizations, particularly in the vulnerable populations of the elderly, the immunocompromised and the obese. The government of Trinidad and Tobago (GoTT) was only able to procure two non-mRNA vaccines: the adenoviral vaccine, AstraZeneca-Vaxzevria (AZ) and the inactivated viral vaccine, Beijing CNBG-BBIBP-CorV/Sinopharm (SP). From February 2021, these vaccines were made available to the public, with preference to special groups including renal transplant recipients (RTRs) [2–4]. Renal transplants have been performed since 2006 in Trinidad and Tobago under the organization of the National Organ Transplant Unit (NOTU). At the time of the study NOTU had performed 195 transplants. August 2021 saw the first mRNA vaccine, Pfizer, being gifted to the country [5], with distribution preference for adolescents. Thus, the majority of the population's primary two-dose immunization, including RTRs, was with non-mRNA vaccines.

In the medical literature, there were reports of between 17 % and 57 % of solid organ transplant recipients (SOTRs) failing to mount adequate antibody responses following two doses with mRNA COVID-19 vaccines [6–8]. Subsequently, recommendations were made by WHO to give this group of patients a 3rd vaccine dose as primary immunization [9,10].

Search of the literature revealed a dearth of information on vaccine

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https://doi.org/10.1016/j.jvacx.2024.100487
Received 20 December 2023; Received in revised form 5 April 2024; Accepted 10 April 2024
Available online 20 April 2024

responses among SOTRs with respect to non-mRNA vaccines. The inactivated viral vaccine and the adenoviral vector vaccine comprised the majority of available vaccines in early 2021 in Trinidad & Tobago. RTRs were among the first members of the national population to receive two-dose primary immunization with one of these two vaccines. However, deaths from SARS-CoV-2 were continuing despite two-dose primary immunization. Since the recommendation of the WHO had not yet been implemented in Trinidad and Tobago, we sought to determine the immune responses to the previously recommended two-dose primary immunization of non mRNA vaccines among our RTRs.

Measurement of anti-spike receptor binding domain (RBD) antibodies does not reflect total immunity to the SARS-CoV-2 virus but has been used as a surrogate marker of potential viral neutralization and immunological protection. It has been widely utilized in studies on vaccine efficacy, including those assessing vaccine responses among SOTR groups [9].

The aim of this study is to contribute information on vaccine humoral responses among the RTRs of Trinidad & Tobago following two-dose primary immunization with either an inactivated viral or adenoviral vector COVID-19 vaccine. Comparisons with regards humoral response will also be demonstrated among other groups including the unvaccinated & uninfected participants.

Methods

Study design and participants

The study was case controlled, using a convenient, voluntary sample. Approval from the relevant ethical committees of the Ministry of Health and the Northwest Regional Health Authority was obtained. Participants were included in the study if they provided proof of vaccination and/or a positive COVID-19 test, gave informed consent, and provided a sample of blood.

The groups were as follows:

Group A (Fig. 1) – Vaccinated RTRs who were all on triple immunosuppressants (IS), a Calcineurin inhibitor, an antiproliferative and steroids.

Group B – Healthy, vaccinated, non-COVID-19-infected participants, who were age and gender matched with RTRs.

Group C – Healthy, non-vaccinated participants with proof of prior COVID-19 infection.

Group D – Healthy, vaccinated participants, with proof of COVID-19 infection, either before or after two-dose primary vaccination.

Group E – Non-vaccinated healthy participants who stated they had not been previously infected with COVID 19.

Study procedure

Blood was collected via venipuncture from 8th November 2021 to 20th December 2021, processed and frozen at −20 °C until time of analysis on 6th January 2022.

Measurement of anti-spike antibodies

Antibodies against the RBD of the spike protein were quantified using the Roche's Elecsys Anti SARS-CoV-2 assay on the COBAS e6001 machine, according to manufacturer's instructions [9]. The assay was donated by Roche International. Results were measured in U/ml with a cut-off 0.8U/mL (manufacturer's recommendation). Samples above 250U/ml were diluted using the ratio ranges 1:10 to 1:100 and reanalyzed.

Statistical analysis

The data was log transformed prior to statistical analyses. To evaluate significant differences between the five groups, an analysis of variance (ANOVA) was performed. Comparison of non-normally distributed data from the groups was assessed with the Wilcoxon test. Correlation calculations were done on the original scale, and the Spearman rank correlation coefficient was applied.

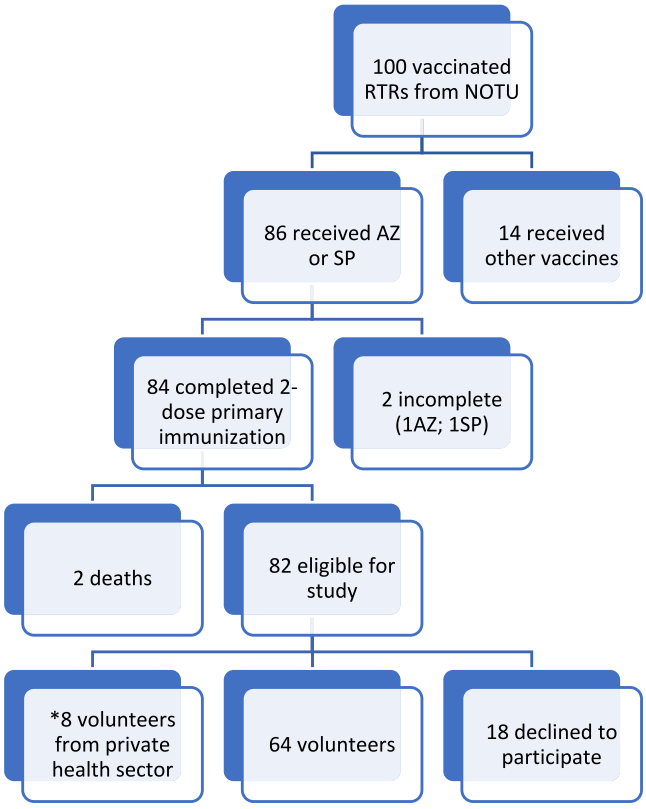

Fig. 1. Recruitment of Renal Transplant Recipients. All vaccinated participants received either AZ or SP.

Results

Baseline characteristics

Of the volunteers, 242 people met inclusion criteria.

There were 123 males and 119 females, age range 19—90 years with a mean age of 46.81 ± 14.81 years. The average age of the RTRs was 49.11 ± 14.59 years.

Vaccinated Participants: 100/171 (58.5 %) received AZ and 71 /171 (41.5 %) received SP. Among the 72 RTRs who volunteered and met the inclusion criteria, 36/72(50 %) received AZ and 36 /72(50 %) received SP.

The highest antibody levels were measured in Group D participants (Fig. 2), who possessed hybrid immunity – combined immunity gained from both vaccination and infection. The response seen in Group A (RTRs) was not significantly different to Group E (unvaccinated, uninfected participants). Among the 72 RTR, only 34/72 (47 %) achieved potential protective levels of anti-spike RBD antibodies. The difference between RTR responses and age- and gender-matched healthy participants was statistically significant $p < 0.05$. The responses of those in Group B and Group C were not significantly different.

In comparing the humoral responses of the RTRs to the two vaccines, the production of antibodies in the AZ vaccinated was greater than the concentration seen in the SP vaccinated (Fig. 3). Since the population was not normally distributed, a Wilcoxon test was performed to determine significance. The p value was < 0.05, thus rejecting the hypothesis that the two vaccines gave the same antibody response.

The above graphs (Fig. 4) illustrate the RTRs response in relation to

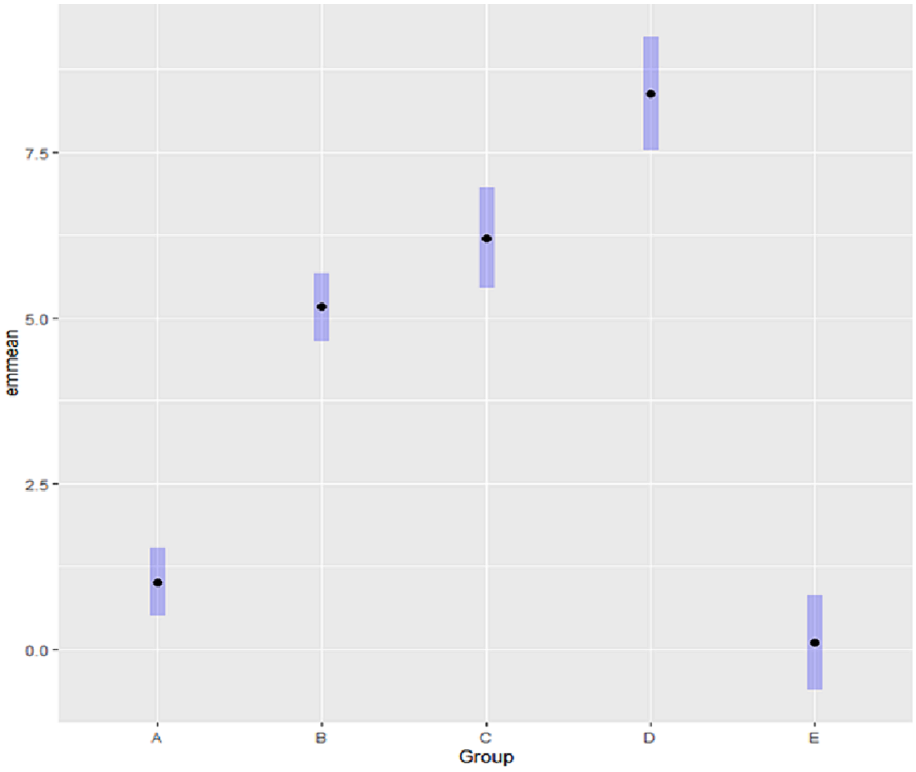

Fig. 2. Anti-spike protein antibody analysis.

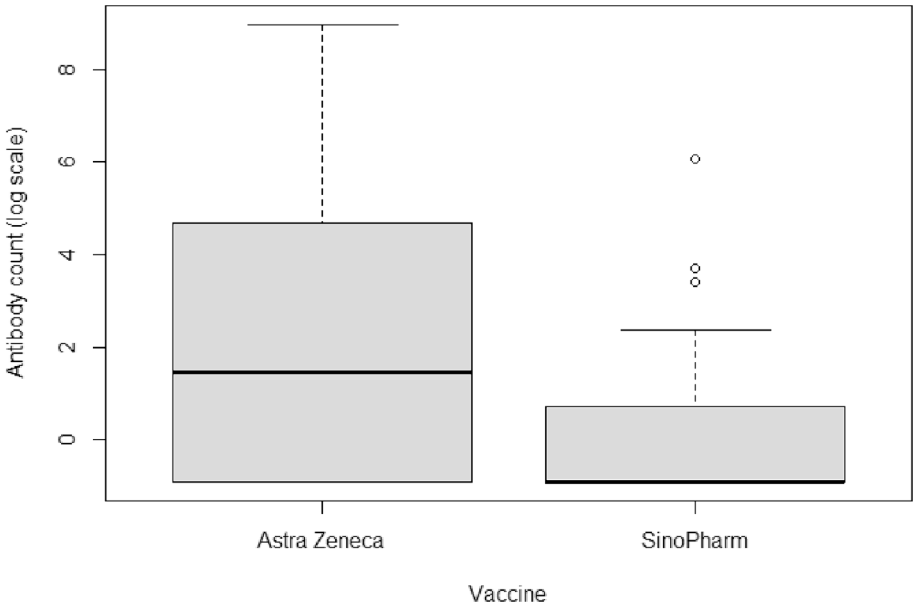

Fig. 3. Comparison of antibody response by SP and AZ for Group A.

timing of their second dose immunization and time post-transplant. The Spearman rank correlation coefficient for the antibody count and the time of the second dose is 0.225. The p value is 0.05724. The Spearman rank correlation coefficient for the antibody count and the time post-transplant is 0.079. The p value is 0.5703. Calculations showed there was no correlation between the antibody level and the time that the second dose was given or the time post-transplant. The statistical significance of the Spearman rank correlation coefficient for both graphs was above $p = 0.05$.

Discussion

Fifty-three percent (38/72) of RTRs failed to make protective levels of anti-spike antibodies following two-dose immunizations with either AZ or SP vaccines. These were the only vaccines available to the general population during the first seven months of 2021 in Trinidad and Tobago, during the height of the COVID-19 pandemic. These findings are consistent with other studies that have shown that SOTRs do not produce antibody levels comparable to those seen in non-transplant recipients after two-dose immunization with mRNA vaccines [7,8].

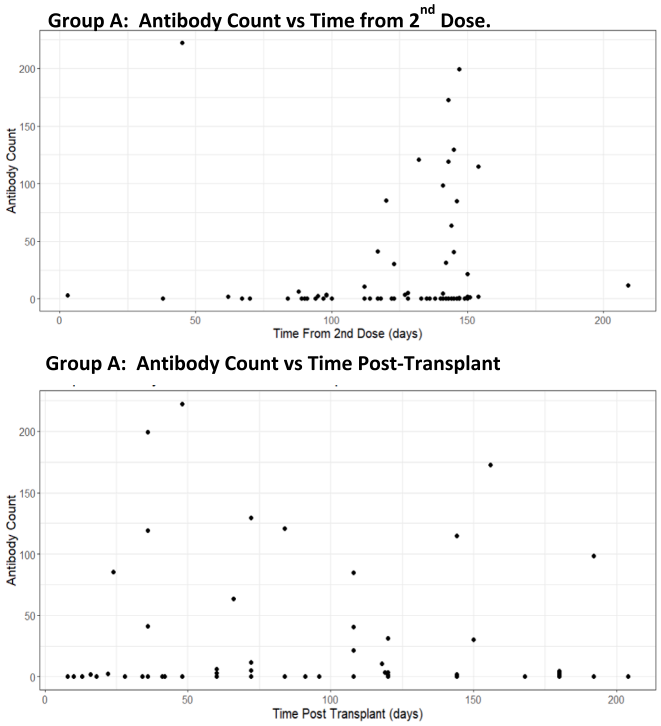

Fig. 4. RTR's response in relation to time from second dose and time post-transplant.

The reasons for poor responses to COVID-19 vaccines reported in SOTRs include older age, closer interval to transplantation and use of antimetabolite therapy such as mycophenolate or biologics such as B-cell depleting monoclonal antibodies [11]. In our study the major factor that may have contributed to the diminished humoral responses was the use of immunosuppressant drugs. All the RTRs were receiving triple immunosuppressants: prednisolone; an anti-proliferative; and a calcineurin inhibitor. While older age has been purported to be a contributing factor for the poor humoral response by SOTRs, the average age in our study was ~ 49 years. As such age may not have significantly contributed to the diminished response seen. In addition, no correlation was evident between antibody production and the time post-transplant given the low Spearman rank correlation coefficient numeric.

Adenovirus vaccines are highly efficacious though less so than the highly immunogenic mRNA vaccines [12]. The efficacy of the inactivated virus vaccine, also administered in Trinidad and Tobago, is less well defined. When we compared the antibody responses among the RTRs, following two-dose immunization with either AZ or SP, we found that antibody levels post-adenovirus vaccine was higher than the post-inactivated viral vaccine and the difference between the two was statistically significant. This, however, does not necessarily translate to overall vaccine efficacy as only one aspect of anti-SARS-CoV-2 humoral immunity was assessed.

Cellular immunity is a critical component in assessing vaccine effectiveness. Hence monitoring of T cell mediated immunity will better inform anti-COVID-19 vaccine strategies in immunocompromised populations where antibody production may be absent or aberrant [13].

Of interest, Group D (vaccinated/infected) had the highest antibody concentration of all the groups. These results indicated the strength of hybrid immunity among participants at the time of testing. Humoral responses of RTRs were most similar to Group E (unvaccinated, uninfected), suggesting that our RTRs were no better protected than the uninfected, unvaccinated individuals.

Since the completion of this study, the RTRs have received at least a third vaccine dose, in keeping with WHO recommendations, some with the Pfizer mRNA vaccine, which became available to the general population in late 2021. Reports in the medical literature show improved anti-COVID-19 humoral responses after third and fourth booster vaccines and especially after heterologous vaccination [14,15]. In this regard, we note that our patients may provide a unique group as many have had mixed vaccinations i.e., primary immunization with either an adenoviral vector vaccine or an inactivated virus vaccine and a mRNA booster. These combinations differ from the reported vaccination schedules of most SOTRs in developed countries [16] and we hope to evaluate our unique RTR population further.

Important limitations of this study included the small number of RTRs and the fact that this was a convenient voluntary study. We solicited NOTU and all the local nephrologists to recruit RTRs, so that our participants could be representative of the national transplant population. Several RTRs, who declined to participate in the study cited fear of entering our busy hospitals where sample collection was undertaken. Increased foot traffic at hospitals after the national lockdown was eased enhanced their fears.

Another limiting factor was the lack of objective testing of prior infection using the anti-nucleocapsid antibody as the test was not available to us at the time. This would have confirmed any prior or recent COVID-19 infections in all participants.

Many of the RTRs have now received their third dose primary immunization and it would be interesting to determine any further changes in their humoral response and compare these changes in relation to which of the two vaccines they received initially.

This paper contributes to the medical literature regarding COVID-19 vaccine responses in a population of RTRs post two-dose immunization with two different non-mRNA vaccines.

CRediT authorship contribution statement

Lesley Roberts: Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Conceptualization. **Carla-Maria Alexander:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation. **Michele Monteil:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Madhura Manjunath:** Writing – review & editing, Investigation. **Emile Mohammed:** Writing – review & editing, Methodology. **Valerie Wilson:** Writing – review & editing, Validation, Methodology. **Stefan Wilson:** Writing – review & editing, Formal analysis.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Lesley Roberts reports supplies was provided by Roche. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

Acknowledgements

The Authors would like to thank the members of Staff of the National Organ Transplant Unit, The Port of Spain General Hospital Laboratory, and the House officers at the Port-of-Spain General Hospital and the St. James Medical Complex who assisted in the conduct of this study.

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